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Inventors: **Huber et al.**
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REMARKS

Claims 51-76, 79-81, 84-92, 95 and 97 are pending in this application. Claims 51-76, 79-81, 84-92, 95 and 97 have been rejected. No new matter has been added by this amendment. A Replacement Information Disclosure Statement with copies of references cited is provided herewith in accordance with the Examiner's request because the references are missing from the PTO file. Reconsideration is respectfully requested in light of the following remarks and amendments.

I. Rejection under 35 U.S.C. 102(a)/103(a)

A. Gusev as Primary Reference

Claims 51-76, 79-81, 84-92, 95 and 97 remain rejected under 35 U.S.C. 102(a) as anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over Gusev et al. (1999) *J. Chromatography*, pg. 273-290. The claims are suggested to read on Gusev et al. and it would have been obvious to optimize the elements of Gusev et al. to enhance separation.

Claims 57-58 and 66 also remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gusev et al. in view of Peters (U.S. Patent No. 5,929,214) for the reasons of record. The Examiner acknowledges that Gusev et al. fail to teach channels sufficiently large to allow convective flow; however, Peters discloses large channels allowing for convective flow and high flow rates through a monolith.

Claim 91 remains rejected under 35 USC 103(a) as being unpatentable over Gusev in view of Girot (US Patent 6,045,697). It is acknowledged that Gusev et al. do not recite the use of a

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tetrahydrofuran porogen; however, Girot discloses that tetrahydrofuran is a suitable porogen.

Claim 95 remains rejected under 35 USC 103(a) as being unpatentable over Gusev, in view of either Huber ((1998) *Anal. Chem.* 70:5288-95) or Griffey ((1997) *J. Mass. Spec.* 32:305-13). It is suggested that the claim differs from Gusev in reciting use of a mass spectrometer. It is suggested that Huber discloses electrospray mass spectrometry and Griffey discloses that electrospray mass spectrometry is a gentle sensitive method of analysis.

The Examiner suggests that Applicants' affidavit submitted with the response dated March 25, 2004 fails to establish Applicants' reduction to practice of the instant invention. It is suggested that the declaration does not state that the work was performed in a U.S., a NAFTA country or a WTO country. It is further suggested that the declaration does not indicate that the monolith was in a fused silica tube having a diameter in the range of 1 to 1000 micrometers, the chromatographic surfaces were non-polar, or that the matrix was underderivatived. Applicants respectfully disagree and traverse these rejections.

At the time the experimental results of the affidavit were being conducted (*i.e.*, August 1998 to February 1999), Applicants were located at the Institute of Analytical Chemistry and Radiochemistry in Innsbruck, Austria, a recognized WTO member country since January 1, 1995. In corroboration of where the disclosed experiments were performed, Applicants submit herewith Huber & Premstaller (received February 19, 1999; published July 16, 1999) *J. Chromatography A* 849:161-173 (abstract) which indicates

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that Applicants were conducting research related to that of the instant application in Innsbruck, Austria at the time in question.

Moreover, Applicants disagree with the Examiner's suggestion that the notebook fails to indicate that the monolith was in a fused silica tube having a diameter in the range of 1 to 1000 micrometers, the chromatographic surfaces were non-polar, or that the matrix was underivatized. The instant specification teaches that poly(styrene-divinylbenzene), also referred to as PS-DVB, is underivatized and has a nonpolar chromatographic surface. See page 17 (lines 30-32) and page 22 (lines 25-27). In this regard, the fourth page of the experimental results provided in the affidavit indicates that the monolith used in the disclosed chromatographic separations of August 1998 was PS-DVB (see legend of chromatograph at the bottom right-hand corner). Accordingly, the notebook pages demonstrate that Applicants were diligently reducing to practice the use of monoliths having an underivatized matrix with nonpolar chromatographic surfaces prior to the effective date of Gusev et al., i.e., September 3, 1999. Further, page 28 (lines 25-27) of the specification indicates that polyimide-coated fused silica capillary tubing is available from Polymicro Technologies (Phoenix, AZ). In this regard, line 7 of the last page of the experimental results provided in the affidavit indicates that a 6 cm TSP025375 column was employed in February 1999 for chromatographically separating dT₁₂ to dT₁₈ oligonucleotides in monolith (see page header and graphs). Polymicro Technologies product literature indicates that TSP025375 is a fused silica tube having an inner diameter of 25 µm and outer diameter of 363 µm. See product literature enclosed herewith. As such, Applicants were actively reducing to practice the use of a polymeric monolith in a fused silica tube having an

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inner diameter in the range of 1 micrometer to 1000 micrometer prior to the effective date of the Gusev reference.

Accordingly, in addition to failing to teach the instant invention (*i.e.*, the use of channels sufficiently large to allow convective flow and the use of a tetrahydrofuran porogen), Gusev et al. is not a proper prior art reference under 35 U.S.C. 102(a), as the present invention was invented prior to the publication of Gusev et al., as evidenced by Applicants' affidavit submitted with the response dated March 25, 2004. Because the secondary references of Peters, Huber, Griffey and Girot fail to teach or suggest all of the claim limitations of the present invention, the instant invention is neither anticipated nor obvious in view of Gusev et al., Peters, Huber, Griffey and Girot. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

B. Frechet or Hatch as Primary Reference

Claims 51-66, 71, 73-76, 79-81, 84-85 and 95 remain rejected under 35 USC 103(a) as being unpatentable over either Frechet U.S. Patent No. 5,344,310) or Hatch (U.S. Patent No. 6,238,565) in view of Peters ((1997) *Anal. Chem.* 69:3646-49), Huang ((1997) *J. Chromatography* 788:155-64) and Tomer ((1994) *Mass. Spec. Rev.* 13:431-57) for the reasons of record.

Claims 67-70 and 72 remain rejected under 35 U.S.C. 103 (a) as being unpatentable over either Frechet or Hatch in view of Peters and Huang for the reasons of record.

Claims 86-92 and 97 remain rejected under 35 U.S.C. 103 (a) as being unpatentable over either Frechet or Hatch in view of Peters and Tomer for the reasons of record.

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Claims 57-58 and 66 remain rejected under 35 USC as being unpatentable over either Frechet or Hatch in view of Peters, Huang and Tomer as applied to claims 51-66, 71, 73-76, 79-85 and 95 above, and further in view of Peters (Patent '214) for the reasons of record.

Claim 91 remains rejected under 35 U.S.C. 103(a) as being unpatentable over either Frechet or Hatch in view of Peters and Tomer as applied to claims 86-92 and 97 above and further in view of Girot for the reasons of record.

Claim 95 remains rejected under 35 U.S.C. 103(a) as being unpatentable over either Frechet or Hatch in view of Peters, Huang and Tomer as applied to claims 51-66, 71, 73-76, 79-85 and 95 above, and further in view of Huber or Griffey for the reasons of record.

Applicants respectfully traverse these rejections.

At the outset, Applicants respectfully point out that, as indicated above, Applicants were actively reducing to practice the use of a polymeric monolith in a fused silica tube having an inner diameter in the range of 1 micrometer to 1000 micrometer prior to the effective date of Hatch, September 16, 1998. Therefore, Hatch cannot be considered to be a valid prior art reference.

Further, MPEP 2143.01 indicates that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

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Applicants respectfully disagree with the Examiner's suggestion that the teachings of Frechet or Hatch in view of Peters provide a sufficient basis for establishing a prima facie case of obviousness in accordance with MPEP 2143.01. At the outset, these references fail to teach or suggest combining or modifying the teachings therein. While Hatch and Frechet teach column matrices composed of poly(styrene-divinylbenzene), nowhere in the teachings of Frechet or Hatch do Applicants find reference to a fused silica tube or covalent attachment of the matrix to the inner wall of the tube. Moreover, while Peters teaches a fused-silica capillary tube containing rigid monoliths composed of ethylene dimethacrylate, butyl methacrylate, and 2-acrylamido-2-methyl-1-propanesulfonic acid, this reference fails to teach or suggest a poly(styrene-divinylbenzene) matrix or covalent attachment of the matrix to the inner wall of the tube. See Abstract and Experimental Section. In point of fact, Peters teaches that their rigid monoliths, in contrast to soft gels, "are not compressible, do not change their size substantially on swelling, and do not require chemical anchoring to the walls of the column." [emphasis added] See page 3647, column 1, lines 4-7. Accordingly, Peters expressly dissuades the skilled artisan from modifying the teachings therein because their rigid monoliths "do not require chemical anchoring to the walls of the column" and can easily achieve "an efficiency higher than 120 000 plates/m." See last sentence of the abstract. Thus, there is no teaching, suggestion or motivation to combine the monolithic poly(styrene-divinylbenzene matrix of Hatch or Frechet with the fused-silica tube of Peters, wherein the monolith is covalently attached to the fused silica tube as disclosed by Huang. In so far as Tomer teaches column dimensions, Peters (Patent '214)

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teaches flow rates, Girot teaches tetrahydrofuran as a porogen, and Huber or Griffey teach EMS, these references fail to overcome the deficiencies in Frechet or Hatch in view of Peters. Thus, these references cannot be held to make obvious the methods of the present invention. It is therefore respectfully requested that the rejection of these claims be reconsidered and withdrawn.

II. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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